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Dimerization of *o*-Hydroxycyclohexadienones Related to Calicheamicinone: S_N2 Displacement of the 12α-Hydroxyl Group

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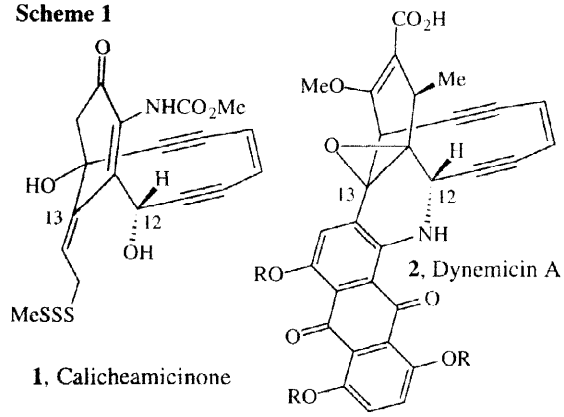
Abstract: Deprotection of the readily available bicyclo[7.3.1]enediyne alcohol **14** resulted in dimerization to give **18**. Replacement of the 12α-hydroxyl group with a *p*-methoxyanilino group proceeded with overall retention to give **23** which also produced a dimer on attempted deprotection.

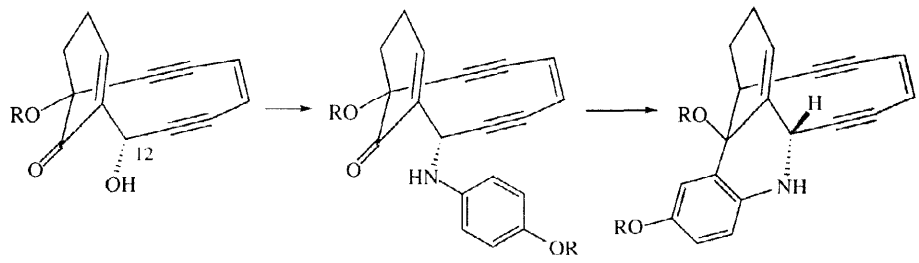
Keywords: Calicheamicinone, dynemicin, dimer, hydroxycyclohexadienone.

Introduction

Scheme 1



In 1987 the Lederle group reported the structure of calicheamicinone **1**, the aglycon of calicheamicin γ_1 isolated from fermentations of *Micromonospora echinospora* sp. calichensis.[1,2] The isolation and structural elucidation of dynemicin A **2** (R = H) was reported in 1989.[3] It was the first enediyne antitumor agent whose structure **2** (R = Ac) was confirmed by X-ray crystallography.[4,5] The source of **1** was the fermentation broth of a new *Micromonospora* strain, isolated from a soil sample collected in Gujarat State, India, and identified as *Micromonospora chersina* sp. nov. No. M956-1. While there has been a substantial amount of literature reporting the syntheses of both **1** and **2**,[6,7] there are no reports of the structural relationship between **1** and **2**. If we draw **1** and **2** in the same orientation, as in **Scheme 1**, replacement of the 12α-hydroxyl group by an anilino moiety with retention of configuration could provide a potential method to convert calicheamicinone-type structures into dynemicin analogues, **Eqn 1**.



Eqn 1

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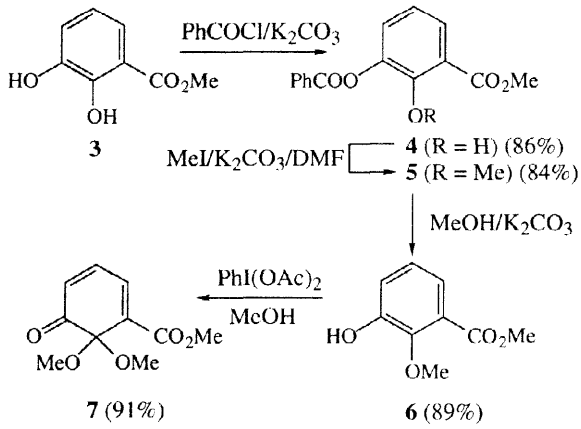
Results

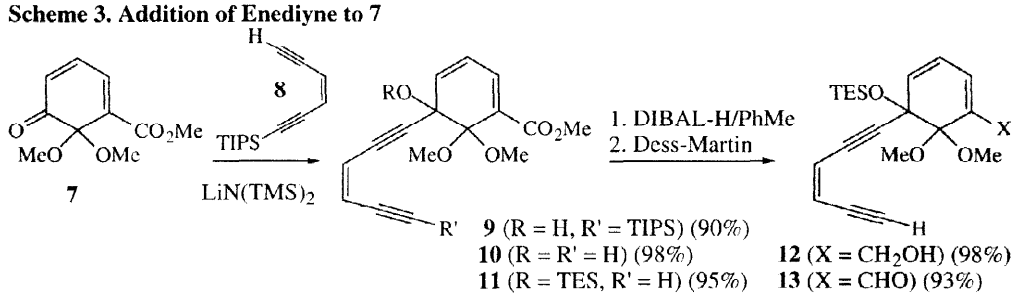
The first requirement was to develop a convenient, large scale synthesis of the *o*-quinone monoketal **7**. The known salicylic ester derivative **3**[8] was converted into the benzoate **4**, and *O*-methylated to give **5**, **Scheme 2**. Mild basic hydrolysis of **5** provided **6**.[9] Treatment of **6** with $PhI(OAc)_2$ in methanol[10] gave **7** as yellow crystals.

Scheme 2. Synthesis of Quinone Monoketal 7



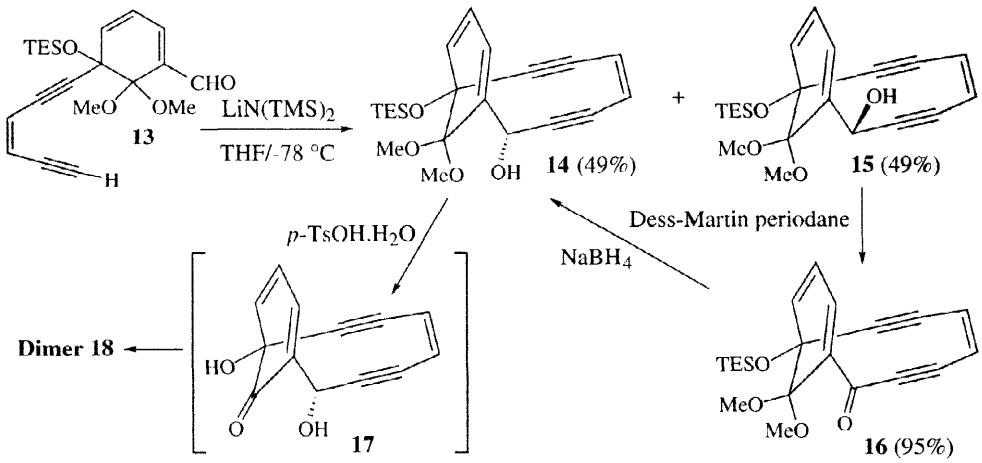
It was discovered that introduction of the enediyne was best accomplished in a single operation making use of the known silyl enediyne **8**.[11] Treatment of **8** with $LiN(TMS)_2$ followed by addition of **7** at -78 °C, and warming to -30 °C gave **9** (90%). Exposure of **9** to tetra-*n*-butylammonium fluoride/THF at 0 °C gave **10**, which was immediately converted into **11** by treatment with triethylsilyl trifluoromethanesulfonate/2,6-lutidine. Reduction of **11** using DIBAL-H in toluene cleanly gave **12**, which could be oxidized with Dess-Martin (D-M) periodinane[12] to give the aldehyde **13** , **Scheme 3**.

Scheme 3. Addition of Enediyne to 7

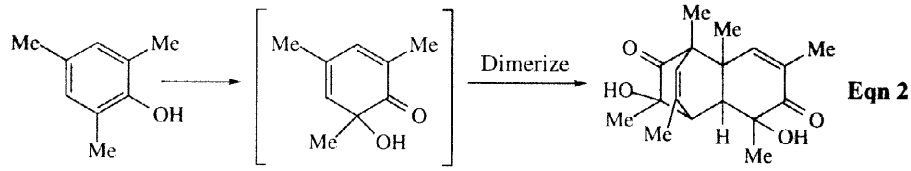


Exposure of **13** to $LiN(TMS)_2$/THF at -78 °C gave **14** and **15** (1:1, 98%), as readily separable crystalline solids. The 12β-alcohol **15** was oxidized using the Dess-Martin periodinane to give the ketone **16**, which was reduced with $NaBH_4/MeOH/CH_2Cl_2$ providing **14** (97%), **Scheme 4**.

Scheme 4. Cyclization to the Bicyclo[7.3.1]enediyne Core



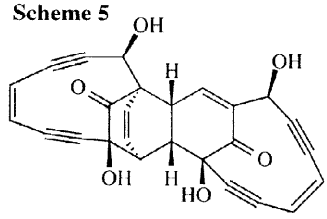
Attempted removal of the protecting groups from **14**, with the expectation that this would result in **17**, gave a dimer **18** as a single diastereomer. The dimerization of *o*-hydroxycyclohexadienones is a well documented reaction, although the stereochemical outcome has remained elusive.[13] Oxidation of **19** with periodate produces the *o*-hydroxycyclohexadienone **20**, which was not isolated, but dimerized to give **21**. The reaction represented in **Eqn 2** shows the regiochemical outcome.



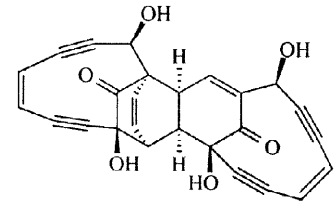
19 **20** **21** **Eqn 2**

A considerable effort was expended to obtain X-ray quality crystals of **18**, but without success. Since **18** is a single regio- and stereoisomer (racemic), we can reduce the number of possible structures to the series shown in **Scheme 5**. Considering the possible *endo*- and *exo*- transition states for the dimerization of **17** into **18**, there are (-)/(+) and (-)/(-) combinations and the corresponding mirror image versions. The products resulting from these arrangements are **18**, **18a**, **18b** and **18c**. MM2 energy minimization of each structure revealed that the *endo*-adduct from the (-)/(+) or (+)/(-) combination, namely **18** (or mirror image), is substantially lower in strain energy (SE kcal mol^{-1}) than the other stereoisomers. Therefore it appears that **18** is most plausible structure for the dimer.

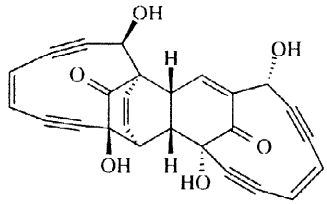
Scheme 5



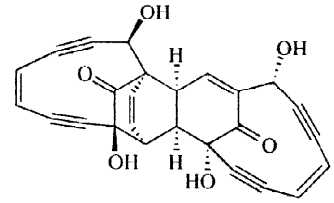
18 (-)/(+) or (+)/(-) *Endo* (SE 40.3)



18a (-)/(+) or (+)/(-) *Exo* (SE 44.1)



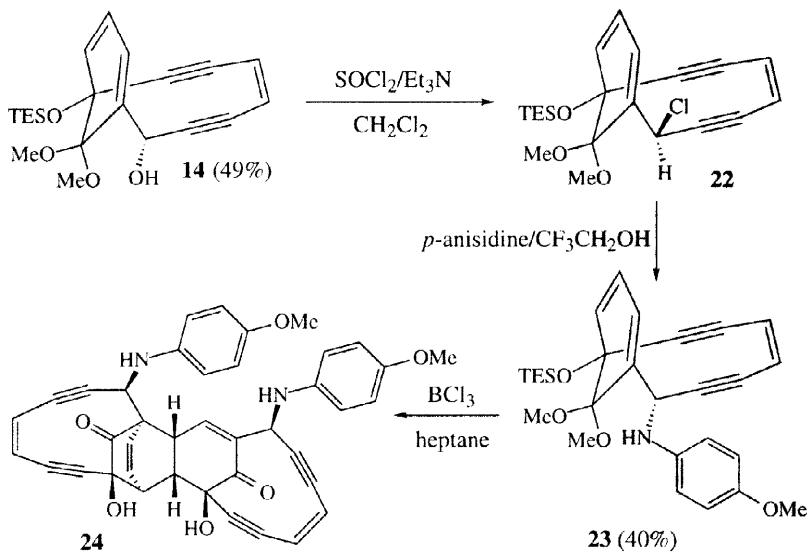
18b (-)/(-) or (+)/(+) *Endo* (SE 46.5)



18c (-)/(-) or (+)/(+) *Exo* (SE 46.3)

The 12α-alcohol **14** is quite sterically hindered, and also capable of propargylic-allenic rearrangement chemistry. Therefore we approached the conversion of **14** into **23** with some considerable reservations as to the viability of this sequence.[14] In the event, it was found that treatment of **14** with thionyl chloride/Et_3N gave **22**, which was immediately exposed to *p*-anisidine in trifluoroethanol to give **23**, **Scheme 6**. The stereochemistry of **23** was confirmed by X-ray analysis.[15] The conversion of **14** into **22** proceeds with inversion. Attempts to deprotect the dimethoxyacetal in **23** under reaction conditions that might also lead to ring closure, as depicted in **Eqn 1**, resulted in the dimer **24** (70%). The structure of **24** is assigned by analogy with **18**.

Scheme 6



Experimental Section

Methyl 2,3-dihydroxybenzoate 3. A 1 litre, three-necked flask fitted with a pressure equalizing dropping funnel and a reflux condenser was charged with 2,3-dihydroxybenzoic acid (100 g, 0.65 mol) and anhydrous MeOH (350 mL). The resulting suspension was cooled to 0 °C and treated with thionyl chloride (50 mL, 0.69 mol), added dropwise over 30 min. The mixture was heated at 50 °C for 16 h. After cooling to ambient temperature the MeOH was evaporated *in vacuo* to give a brown solid. The solid was dissolved in EtOAc (1.5 l) and washed with pH 7.4 buffer (1 l), water (2 x 1 L), brine (1 l), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave **3** (103 g, 94%).[8,9] ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (3H, s), 5.65 (1H, br s), 6.80 (1H, t, J = 8.0 Hz), 7.11 (1H, dd, J = 8, 1.5 Hz), 7.36 (1H, dd, J = 8, 1.5 Hz), 10.89 (1H, br s).

Methyl 3-benzoyloxy-2-hydroxybenzoate 4. A solution of **3** (51 g, 0.30 mol) in dichloromethane (400 mL) was treated with K_2CO_3 (44 g, 0.32 mol) and the resulting suspension cooled to 0 °C. A solution of benzoyl chloride (43 g, 0.31 mol) in dichloromethane (50 mL) was added over a period of 5 min, and the mixture was stirring at 0 °C for 90 min. Water (750 mL) was added and the mixture stirred to ambient temperature. The organic phase was separated, washed with pH 7.4 buffer (300 mL), water (300 mL), brine (300 mL) and dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo* gave the crude product as a brown solid. Trituration with a 5% solution of water in MeOH and filtration gave **4** (71 g, 86%) as a tan solid. A small sample was recrystallized from hexanes/Et_2O to give **4** as colorless needles. mp 78-79 °C.[8,9] ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (3H, s), 6.93 (1H, t, J = 8.0 Hz), 7.38 (1H, dd, J = 8, 1.5 Hz), 7.52 (2H, m), 7.64 (1H, m), 7.78 (1H, dd, J = 8, 1.5 Hz), 8.25 (2H, m), 10.97 (1H, br s).

Methyl 3-benzoyloxy-2-methoxybenzoate 5. A solution of **4** (71 g, 0.26 mol) in anhydrous *N,N*-dimethylformamide (250 mL) was treated with K_2CO_3 (42 g, 0.30 mol), added in two portions over 5 min followed by iodomethane (20 mL, 0.32 mol). The resulting suspension was stirred vigorously at 35 °C for 90 min and cooled to ambient temperature. The liquid was decanted from the solid residues and the majority of

the solvent evaporated *in vacuo* to give a dark brown slurry. The solid residue was dissolved in water (500 mL), combined with the slurry, and the product extracted with Et_2O (750 mL). The organic phase was washed with water (2 x 500 mL), brine (500 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent *in vacuo* gave the crude product as a brown solid. Recrystallization from heptane/Et_2O gave **5** (63 g, 84%) as colorless prisms.[8,9] ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.92 (3H, s), 7.20 (1H, t, J = 8.0 Hz), 7.38 (1H, dd, J = 8.0, 1.5 Hz), 7.53 (2H, m), 7.67 (1H, m), 7.74 (1H, dd, J = 8, 1.5 Hz), 8.23 (2H, m).

Methyl 3-hydroxy-2-methoxybenzoate 6. A solution of **5** (67 g, 0.23 mol) in MeOH (250 mL) was treated with K_2CO_3 (65 g., 0.47 mol), and the resulting suspension was stirred at ambient temperature for 3 h. The liquid was decanted from the solid residues and the solvent evaporated *in vacuo* to give an oil. The solid residues were dissolved in water (300 mL) and acidified to pH 2 with 36% HCl. The aqueous solution was combined with the oil and the product extracted with Et_2O (750 mL). The organic phase was washed with water (500 mL), brine (500 mL), and dried ($MgSO_4$). Filtration and evaporation *in vacuo* gave a brown oil which was purified in two batches by chromatography over silica gel eluting with 10-30% EtOAc/hexanes to give **6** (38 g, 89%) as a colorless oil.[8,9] ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 3.92 (3H, s), 5.99 (1H, br s), 7.04 (1H, t, J = 8.0 Hz), 7.14 (1H, dd, J = 8, 1.5 Hz), 7.38 (1H, dd, J = 8, 1.5 Hz).

Methyl 2,2-dimethoxy-3-oxo-cyclohexa-4,6-diene-1-carboxylate 7. To a solution of **6** (25 g, 0.14 mol) in MeOH (300 mL) at 0 °C was added iodobenzene diacetate (45 g, 0.14 mol) in one portion. The mixture was stirred at 0 °C for 30 min, water (10 mL) was added, and the MeOH evaporated *in vacuo*. The residue was dissolved in EtOAc (400 mL) and washed with pH 7.4 buffer (300 mL), water (300 mL), brine (300 mL), and dried (Na_2SO_4). Filtration and evaporation *in vacuo* to dryness gave a yellow oil which solidified under high vacuum. The solid was triturated with pentane and filtered at the pump to give **7** (26.5 g, 91%) as a bright yellow powder. mp 66-67 °C. IR (thin film) 2989, 2946, 2837, 1729, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.28 (6H, s), 3.84 (3H, s), 6.26 (1H, dd, J = 10.0, 1.0 Hz), 6.99 (1H, dd, J = 10, 6.0 Hz), 7.32 (1H, dd, J = 6.0, 1.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1, 52.2, 93.9, 129.6, 134.6, 137.5, 138.0, 163.6, 194.9. HRMS (CI) calcd for $C_{10}H_{12}O_5$ (M^+) 212.0685, found 212.0677.

Methyl 2,2-dimethoxy-3-hydroxy-3-[(Z)-6-triisopropylsilylhexa-1,5-diyne-3-ene]cyclohex-4,6-diene-1-carboxylate 9. A solution of 1,1,1,3,3,3-hexamethyldisilazane (11.5 mL, 55 mmol) in tetrahydrofuran (75 mL) was cooled to -20 °C and treated with *n*-butyl lithium (21 mL of a 2.5 M solution in hexanes, 53 mmol). After stirring the mixture at -20 °C for 5 min the solution was cooled to -78 °C, and treated with a pre-cooled (-78 °C) solution of **8** (11.5 g, 49 mmol) in tetrahydrofuran (75 mL). The mixture was stirred at -78 °C for 15 min, and a pre-cooled (0 °C) solution of ketal **7** (10 g, 47 mmol) in tetrahydrofuran (100 mL) was added to the solution of the lithioacetylide formed above by means of a double-ended needle over a period of 5 min. The resulting mixture was stirred at -78 °C for 45 min, and quenched with a 5% aqueous tetrahydrofuran (100 mL). After stirring the mixture to ambient temperature the majority of the tetrahydrofuran was evaporated *in vacuo*, and the residue dissolved in EtOAc (500 mL), and washed with 0.1 N HCl (300 mL), water (300 mL), brine (300 mL), and dried (Na_2SO_4). Filtration and evaporation *in vacuo* gave a brown oil which was purified by chromatography over neutral alumina containing 10% w/w water eluting with 0-30% EtOAc/hexanes to

give **9** (18.9 g, 90%) as a yellow oil. IR (thin film) 3482, 2946, 2857, 2143, 1724 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 1.15-1.25 (21H, m), 3.27 (1H, br s), 3.35 (3H, s), 3.47 (3H, s), 3.56 (3H, s), 5.45-5.50 (3H, m), 6.10 (1H, dd, J = 9.0, 1.0 Hz), 6.52 (1H, dd, J = 5.5, 1.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 11.6, 18.9, 51.5, 51.8, 51.9, 73.7, 82.5, 95.6, 99.6, 100.1, 104.4, 120.1, 120.2, 120.7, 131.5, 133.8, 140.4, 166.0. HRMS (CI) calcd for $C_{25}H_{36}O_5Si$ (M^+) 444.2332, found 444.2333.

Methyl 2,2-dimethoxy-3-hydroxy-3-[(Z)-hexa-1,5-diyne-3-ene]cyclohex-4,6-diene-1-carboxylate 10. A solution of **9** (5.0 g, 11.2 mmol) in tetrahydrofuran (100 mL) was cooled to 0 °C and treated with tetra-*n*-butylammonium fluoride (17.0 mL of a 1.0 M solution in tetrahydrofuran, 17.0 mmol) added dropwise by syringe over 5 min. After a further 5 min, MeOH (5 mL) and water (5 mL) were added. The solvent was evaporated *in vacuo*, and the residue dissolved in EtOAc (250 mL), washed with 0.1 N HCl (200 mL), water (200 mL), brine (200 mL), and dried (Na_2SO_4). Filtration and evaporation to dryness gave a brown oil which was purified by chromatography over silica gel eluting with 10-30% EtOAc/hexanes to afford **10** (3.19 g, 98%) as a pale yellow oil. IR (thin film) 3472, 3264, 2946, 2083, 1719 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 2.95-2.97 (1H, m), 3.30 (1H, br s), 3.35 (3H, s), 3.47 (3H, s), 3.56 (3H, s), 5.28 (1H, dd, J = 11.5, 2.0 Hz), 5.39-5.44 (2H, m), 6.03 (1H, dd, J = 9.5, 1.5 Hz), 6.50 (1H, dd, J = 6.0, 1.5 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 51.6, 51.9, 52.0, 73.7, 80.8, 82.0, 85.7, 95.7, 100.1, 119.7, 120.9, 121.2, 131.6, 133.9, 140.3, 166.1. HRMS (CI) calcd for $C_{16}H_{16}O_5$ (M^+) 288.0998. Found 288.0987.

Methyl 2,2-dimethoxy-3-(triethylsilyl)oxy-3-[(Z)-hexa-1,5-diyne-3-ene]cyclohex-4,6-diene-1-carboxylate 11. A solution of **10** (3.1 g, 11 mmol) and 2,6-lutidine (1.9 mL, 16 mmol) in dichloromethane (30 mL) was cooled to 0 °C, and treated with triethylsilyl trifluoromethanesulfonate (2.8 mL, 12 mmol). After stirring the mixture at 0 °C for 45 min the reaction was quenched with 0.1 N HCl (50 mL), and the organic phase was separated. The aqueous phase was extracted with dichloromethane (100 mL), and the combined extracts were washed with 0.1 N HCl (100 mL), water (100 mL), brine (100 mL) and dried (Na_2SO_4). Filtration and evaporation to dryness gave a yellow oil which was purified by chromatography over silica gel eluting with 0-15% EtOAc/hexanes to furnish **11** (4.1 g, 95%) as a colorless oil. IR (thin film) 3258, 2948, 2873, 1724 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.72-0.83 (6H, m), 1.04-1.10 (9H, m), 2.88 (1H, dd, J = 2.5, 1.0 Hz), 3.36 (3H, s), 3.59 (3H, s), 3.76 (3H, s), 5.30 (1H, dd, J = 12.0, 2.5 Hz), 5.45-5.55 (2H, m), 6.16 (1H, dd, J = 9.5, 1.0 Hz), 6.45 (1H, dd, J = 5.5, 1.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 6.7, 7.2, 51.4, 51.5, 52.4, 72.0, 81.1, 83.2, 85.0, 99.5, 101.0, 119.1, 121.2, 121.8, 131.6, 134.0, 139.0, 166.3. HRMS (CI) calcd for $C_{22}H_{31}O_5Si$ (M+1) 403.1941. Found 403.1928.

2,2-Dimethoxy-3-(triethylsilyl)oxy-3-[(Z)-hexa-1,5-diyne-3-ene]cyclohex-4,6-diene-1-carbinol 12. To a stirred solution of **11** (5.7 g, 14.2 mmol) in toluene (70 mL) at -78 °C was added a pre-cooled (-78 °C) solution of diisobutylaluminum hydride (35 mL of a 1.0 M solution in toluene, 35.0 mmol) by means of a double-ended needle. The mixture was stirred at -78 °C for 1.5 h, and quenched with MeOH (5 mL), followed by powdered $Na_2SO_4.10H_2O$ (20 g), and the mixture stirred vigorously to ambient temperature over 45 min. The mixture was filtered through Celite™, the filter cake washed with EtOAc (100 mL), and the solution evaporated *in vacuo* to give a yellow oil. The oil was dissolved in EtOAc (250 mL), and washed with 0.1 N

HCl (150 mL), water (150 mL), brine (150 mL), and dried (Na_2SO_4). Filtration and evaporation to dryness gave **12** (5.22 g, 98%) as a yellow oil, which was used without further purification. IR (thin film) 3425, 3295, 2955, 2872 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.72-0.87 (6H, m), 1.04-1.11 (9H, m), 2.23 (1H, dd, J = 7.0, 4.5 Hz), 2.91 (1H, d, J = 2.0 Hz), 3.17 (3H, s), 3.55 (3H, s), 4.18 (1H, dd, J = 13.5, 7.0 Hz), 4.41 (1H, dd, J = 13.5, 4.5 Hz), 5.31 (1H, dd, J = 11.0, 2.5 Hz), 5.47-5.51 (1H, m), 5.61 (1H, dd, J = 9.5, 5.5 Hz), 5.81-5.83 (1H, m), 5.95 (1H, d, J = 9.5 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 6.7, 7.3, 50.8, 64.4, 71.8, 81.2, 82.9, 84.8, 100.0, 101.5, 118.9, 121.4, 122.5, 123.34, 134.1, 140.9 (1 signal absent). HRMS (CI) calcd for $C_{21}H_{30}O_4Si$ (M^+) 374.1913, found 374.1910.

2,2-Dimethoxy-3-(triethylsilyl)oxy-3-[(Z)-hexa-1,5-diyne-3-ene]cyclohex-4,6-diene-1-carboxaldehyde 13. A solution of **12** (3.5 g, 9.3 mmol) in dichloromethane (100 mL) at 0 °C was treated with sodium hydrogen carbonate (1.6 g, 19 mmol), followed by Dess-Martin periodinane (4.16 g, 9.8 mmol), and the mixture was warmed to ambient temperature over 1 h. The mixture was quenched with 1 N aqueous $Na_2S_2O_3$ (5 mL) followed by saturated aqueous $NaHCO_3$ (5 mL). The solvent was evaporated *in vacuo*, and the residue shaken with EtOAc (100 mL) and filtered through a plug of neutral alumina (containing 10% *w/w* water) washing the filter cake with EtOAc (50 mL). The filtrate was washed with water (100 mL), brine (100 mL) and dried (Na_2SO_4). Filtration and evaporation *in vacuo* gave **13** (3.2 g, 93%) as a yellow solid which was used without further purification. IR (thin film) 3260, 2955, 2872, 1625 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.65-0.78 (6H, m), 0.98-1.04 (9H, m), 2.89-2.90 (1H, m), 3.09 (3H, s), 3.55 (3H, s), 5.30 (1H, dd, J = 11.0 and 2.0 Hz), 5.46-5.50 (1H, m), 5.52 (1H, dd, J = 9.5, 6.0 Hz), 6.14 (1H, d, J = 9.5 Hz), 6.82 (1H, d, J = 6.0 Hz), 10.15 (1H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 6.6, 7.2, 50.7, 50.9, 71.5, 81.1, 83.2, 85.2, 98.5, 100.6, 119.5, 121.0, 122.2, 131.9, 136.0, 140.6, 190.3. HRMS (CI) calcd for $C_{21}H_{29}O_4Si$ (M+1) 373.1835, found 373.1828.

13,13-Dimethoxy-5-(triethylsilyl)oxy-12α/β-hydroxybicyclo[7.3.1]trideca-6,10-diyn-1,3,8-triene 14 and 15. A solution of 1,1,1,3,3,3-hexamethyldisilazane (0.8 mL, 3.8 mmol) in tetrahydrofuran (30 mL) was cooled to -10 °C and treated with *n*-butyllithium (1.45 mL of a 2.5 molar solution in hexanes, 3.6 mmol). After stirring the solution at -10 °C for 5 min it was treated with a pre-cooled (0 °C) solution of **36** (1.28 g, 3.4 mmol) in tetrahydrofuran (10 mL). The mixture was stirred at -10 °C for 10 min, and quenched with 50% aqueous tetrahydrofuran (10 mL). After stirring to ambient temperature the majority of the tetrahydrofuran was evaporated *in vacuo*, and the residue dissolved in EtOAc (100 mL), and washed with 0.1 N HCl (100 mL), water (100 mL), brine (100 mL), and dried (Na_2SO_4). Filtration and evaporation *in vacuo* gave a brown oil which was purified by flash chromatography over silica gel eluting with 5% EtOAc/hexanes gave the *α-alcohol* **14** (630 mg, 49%) as a pale yellow solid. mp 59-61 °C. IR (thin film) 3510, 2947, 2879 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.71-0.80 (6H, m), 1.02-1.08 (9H, m), 3.18 (3H, s), 3.37 (3H, s), 3.89 (1H, d, J = 12.0 Hz), 5.23-5.33 (2H, m), 5.48-5.55 (2H, m), 5.82 (1H, dd, J = 9.5, 1.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 6.8, 7.3, 50.8, 51.9, 68.4, 78.2, 85.5, 87.6, 98.5, 102.3, 104.2, 122.0, 123.4, 124.4, 125.1, 136.0, 143.5. HRMS (CI) calcd for $C_{21}H_{28}O_4Si$ (M^+) 372.1757, found 372.1754.

Further elution with 15-20% EtOAc/hexanes gave the *β-alcohol* **15** (629 mg, 49%) as a pale yellow solid. mp 92-94 °C. ^1H NMR (300 MHz, C_6D_6) δ 0.75-0.83 (6H, m), 1.04-1.11 (9H, m), 1.48 (1H, d, J = 5.0

Hz), 2.99 (3H, s), 3.51 (3H, s), 5.32 (1H, d, J = 5.0 Hz), 5.45-5.54 (2H, m), 5.74 (1H, dd, J = 9.5, 5.5 Hz), 5.86-5.90 (1H, m), 6.06-6.09 (1H, m).

13,13-Dimethoxy-5-(triethylsilyl)oxy-12-oxobicyclo[7.3.1]trideca-6,10-diyn-1,3,8-triene 16. A solution of **15** (605 mg, 1.6 mmol) in dichloromethane (10 mL) was cooled to 0 °C and treated with $NaHCO_3$ (275 mg, 3.3 mmol) followed by Dess-Martin periodinane (730 mg, 1.7 mmol). The mixture was stirred at room temperature for 1 h, and quenched with 1 N aqueous $Na_2S_2O_3$ (1 mL) followed by saturated aqueous $NaHCO_3$ (1 mL). The solvent was evaporated *in vacuo*, and the residue shaken with EtOAc (20 mL), and filtered through Celite™ washing the filter cake with EtOAc (5 mL). The filtrate was washed with water (25 mL), brine (25 mL) and dried (Na_2SO_4). Filtration and evaporation to dryness gave **16** (572 mg, 95%) as a yellow solid which was used without further purification. mp 95-96 °C (dec). IR (thin film) 2953, 2154, 1674 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.63-0.77 (6H, m), 1.01-1.06 (9H, m), 3.24 (3H, s), 3.43 (3H, s), 5.27 (1H, d, J = 9.5 Hz), 5.42 (1H, dd, J = 9.5, 5.0 Hz), 5.52 (1H, d, J = 9.5 Hz), 5.58 (1H, dd, J = 5.0, 1.0 Hz), 5.83 (1H, dd, J = 9.5, 1.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 6.7, 7.2, 50.7, 51.4, 77.8, 84.7, 99.8, 101.3, 101.6, 103.3, 121.9, 122.4, 122.8, 130.2, 137.2, 147.8, 179.8. HRMS (CI) calcd for $C_{21}H_{26}O_4Si$ (M^+) 370.1600, found 370.1592.

13,13-Dimethoxy-5-(triethylsilyl)oxy-12α-hydroxybicyclo[7.3.1]trideca-6,10-diyn-1,3,8-triene 14. A solution of **16** (572 mg, 1.5 mmol) in MeOH (5 mL) and dichloromethane (5 mL) was cooled to 0 °C and treated with sodium borohydride (150 mg, 4.0 mmol). Stirring was continued for 30 min after which time water (10 mL) was added. The solvent was evaporated *in vacuo*, and the residue taken up in EtOAc (50 mL) and washed with 0.1 N HCl (50 mL), water (50 mL), brine (50 mL), and dried (Na_2SO_4). Filtration and evaporation to dryness gave a yellow foam which was analyzed by ^1H NMR and shown not to contain the undesired β-alcohol **15**. Purification of by chromatography over silica gel eluting with 5-10% EtOAc/hexanes gave **14** (558 mg, 97%) as an off-white solid.

Dimer 18. A solution of **14** (100 mg, 0.27 mmol) in acetone (5 mL) and water (0.5 mL) was treated with *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) at 23 °C for 16 h. The mixture was pre absorbed directly on to silica gel and loaded on to a column. Elution with 10-50% EtOAc/hexanes gave **18** (46 mg, 81%) as a colorless glass that discolored on standing. ^1H NMR (300 MHz, Acetone-d_6) δ 3.24 (1H, d, J = 7.0 Hz), 3.54-3.60 (2H, m), 4.50 (1H, d, J = 6.0 Hz), 4.55 (1H, d, J = 6.0 Hz), 5.00 (1H, d, J = 11.5 Hz), 5.32 (1H, d, J = 9.5 Hz), 5.61 (1H, s), 5.72 (1H, s), 5.94-6.04 (5H, m), 6.22 (1H, dd, J = 8.0, 7.0 Hz), 6.58 (1H, d, J = 4.5 Hz). ^{13}C NMR (75 MHz, Acetone-d_6) δ 42.6, 43.6, 45.3, 60.3, 66.3, 67.9, 73.2, 75.2, 86.1, 87.7, 89.8, 95.7, 99.3, 100.9, 101.1, 102.1, 123.8, 124.0, 124.4, 130.7, 136.1, 138.6, 140.3, 195.0, 208.6. HRMS (CI) calcd for $C_{26}H_{16}O_6$ (M^+) 424.0947, found 424.0945.

13,13-Dimethoxy-5-(triethylsilyl)oxy-12α-(*N*-4-methoxyphenyl)aminobicyclo[7.3.1]trideca-6,10-diyn-1,3,8-triene 23. To a stirred solution of **14** (156 mg, 0.42 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (0.175 mL, 1.3 mmol) and thionyl chloride (0.041 mL, 0.55 mmol) and the mixture stirred for 15 min. To this mixture was added *p*-anisidine (515 mg, 4.2 mmol) and trifluoroethanol (2 mL) and

the mixture stirred at room temperature for 45 min. The deep red solution was applied directly to the top of a column of florisil® and rapidly eluted with ether/petroleum ether (1:4; *v/v*). Evaporation *in vacuo* afforded gave **23** as a colorless oil (80 mg, 40%). IR (thin film) 3371, 2953, 1512, 1132, 1071 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.82 (6H, m), 1.12 (9H, t, *J* = 7.5 Hz), 3.22 (3H, s), 3.39 (3H, s), 3.58 (3H, s), 4.93 (1H, d, *J* = 11.0 Hz), 5.17 (1H, d, *J* = 11.0 Hz), 5.45 (1H, dd, *J* = 9.5, 1.0 Hz), 5.53 (1H, d, *J* = 9.5 Hz), 5.59 (1H, d, *J* = 5.0 Hz), 5.64 (1H, dd, *J* = 9.0, 5.0 Hz), 5.91 (1H, d, *J* = 9.0 Hz), 6.67 (2H, d, *J* = 8.0 Hz), 6.85 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (300 MHz, C_6D_6) δ 6.9, 7.4, 30.2, 50.9, 52.3, 55.2, 55.3, 85.7, 86.6, 98.0, 101.9, 104.2, 115.2, 116.5, 123.8, 124.1, 125.3, 136.2, 141.3, 142.6, 153.7. HRMS (CI) calcd for $C_{28}H_{35}O_4NSi$ (M+1) 477.2335, found 477.2327.

Dimer 24. To a stirred solution of **23** (30 mg, 0.062 mmol) in dichloromethane (3 mL) cooled to -20 °C was added Et_3N (0.088 mL, 0.62 mmol) and boron trichloride (0.19 mL of a 1.0 M solution in heptane, 0.19 mmol) and the solution stirred at -20 °C for 20 min. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (10 mL), warmed to room temperature and the were layers separated. The organic layer was washed with citric acid (5 mL, 0.5 M solution), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to leave a residue which was purified by chromatography over florisil® eluting with Et_2O/petroleum ether (1:1) to give **24** as a colorless oil (19 mg, 70%). IR (thin film) 3362, 2954, 1739, 1709, 1514, 1243, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (12H, m), 1.03 (18H, m), 3.27 (1H, d, *J* = 8Hz), 3.52 (1H, dd, *J* = 7.5, 1.5 Hz), 3.65 (1H, dd, *J* = 8, 5.5 Hz), 3.77 (3H, s), 3.79 (3H, s), 4.46 (1H, d, *J* = 11 Hz), 5.02 (1H, d, *J* = 11 Hz), 5.51 (1H, t, *J* = 11 Hz), 5.72 (2H, s), 5.77 (1H, d, *J* = 10 Hz), 5.80 (1H, d, *J* = 10 Hz), 5.88 (1H, dd, *J* = 7, 1.5 Hz), 6.22 (2H, m), 6.71 (2H, d, *J* = 8.0 Hz), 6.75 (2H, d, *J* = 8.0 Hz), 6.82 (2H, d, *J* = 8.0 Hz), 6.87 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (300 MHz, C_6D_6) δ 6.5, 6.8, 7.4, 7.6, 42.6, 45.3, 47.9, 51.9, 54.9, 55.1, 55.2, 62.8, 75.5, 76.9, 85.1, 91.4, 94.4, 98.7, 101.6, 102.4, 115.0, 115.2, 116.5, 116.8, 121.6, 121.9, 124.4, 124.9, 128.8, 130.8, 135.6, 138.5, 139.1, 140.6, 141.0, 153.9, 154.4, 193.8, 205.8. MS (FAB) 862 (M^+).

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Footnote and References

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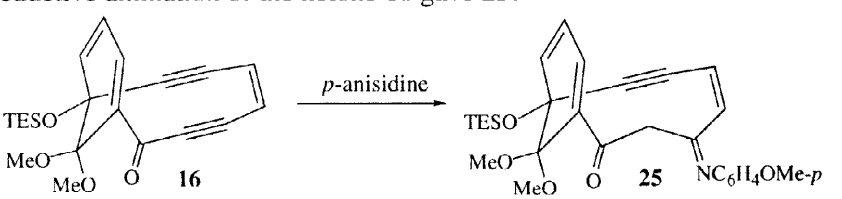
14. Attempted reductive amination of the ketone **16** gave **25**!



15. Full X-ray crystallographic data for **23** has been deposited in the Cambridge data base.